University of Alberta

The Descriptive Epidemiology of Primary Lung Cancer in an Alberta Cohort with a Multivariate Analysis of Survival to Two Years

By

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Abstract

Lung cancer is the leading cause of cancer death and the second most common incident cancer experienced by Canadians. Although lung cancer case fatality rates have not changed significantly over the last decade there have been advances in the diagnosis, staging and management of lung cancer. In order to assess the potential impact of such advances, the experiences of a recent Canadian lung cancer cohort is presented. This thesis reviews the descriptive epidemiology of lung cancer in a 1998 Alberta cohort with a multivariate analysis of factors contributing to survival to two years. The results generally concur with the North American literature. Continued monitoring of the epidemiology of lung cancer is essential to evaluate the impact of advances in the diagnosis, staging and management of lung cancer. Further clinical and economic analysis, based on data collected on this cohort, is planned.

Dedication

I dedicate this thesis to my wife Lois and my son Aaron who both contributed significant family time to allow me to complete this journey.

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Table of contents

1. Introduction..... 1
2. Background..... 1
   2.1. Lung Cancer Epidemiology.....1
   2.2. Lung Cancer Diagnosis 3
      2.2.1. CT Lung Cancer Staging.....3
      2.2.2. CT Lung Cancer Screening.....3
      2.2.3. PET Imaging in Lung Cancer 6
   2.3. Lung Cancer Therapy.....8
3. Methodology.....10
4. Results.....13
   4.1. Descriptive Epidemiology.....13
   4.2. Frequency and Type of Health Care Interventions..... 15
   4.3. Survival Analysis.....15
5. Discussion 16
6. Figures.....22
7. Tables.....26
8. Bibliography.....35
9. Appendix A - Literature Search -Key Word Search Parameters 41
10. Appendix B - Data Abstraction Form.....43
11. Appendix C - NCI,. Non-small Cell Lung Cancer (PDQ®): Treatment 45
12. Appendix D - Sample Cox Regression Analysis Output 48

List of tables

Table 1 An Overview of Information Collected

Table 2 Frequency of Histological Diagnoses

Table 3 Frequency of Stage at Presentation and Percent Survival to Two Years from Date of Diagnosis

Table 4 Interventions Stratified by Type of Lung Cancer and Presenting Stage

Table 5 Frequency of Surgical Interventions (n) by Stage for NSCLC

Table 6 Cox Regression Analysis of Selected Variables for Survival Two Years From Date of Diagnosis

Table 7 Multivariate Cox Regression Analysis of Selected Variables for Survival Two Years From Date of Diagnosis

Table 8 Multivariate Cox Regression Analysis* of Selected Variables in Stage IIIB and IV NSCLC Patients

Table 9 Survival to Two Years by Stage – A Comparison To the Literature

List of figures

Figure 1 Survival to Two Years by Stage - Non-Small Cell Lung Cancer by Stage

Figure 2 Survival to Two Years by Stage – Small Cell Lung Cancer

Figure 3 Interval (days) Between Diagnosis Date and First Attendance at the Cross Cancer Institute

Figure 4 Interval (days) Between Diagnosis Date and Thoracic Surgery

List of symbols nomenclature or abbreviations

AB = Alberta

ACB = Alberta Cancer Board

ACR = Alberta Cancer Registry

CCI = Cross Cancer Institute

CMS = Centers for Medicare and Medicaid Services

CT = computed tomography

FDG = 18 fluorodeoxyglucose

HCFA = Health Care Finance Administration

ICD-O = International Classification of Diseases - Oncology

MRI = magnetic resonance imaging

NCI = National Cancer Institute

NM = Nuclear Medicine

NSCLC = non-small cell lung cancer

PET = positron emission tomography

PYLL = potential years of life lost

SEER = Surveillance Epidemiology and End Results

SCLC = small cell lung cancer

TNM = primary tumor (T)– regional lymph nodes (N)– distant metastasis (M)

USA = United States of America

χ^2= Chi square

1) Introduction:

Lung cancer is the number one cause of cancer mortality and it is t
ıe second most common incident cancer in Canada. This thesis describes the epid
:miology of a 1998 Northern Alberta lung cancer patient cohort with a multivariate su
vival analysis censored at two years from the date of diagnosis, or death, whiche
/er came first. This work will establish a timely and comprehensive epidemiological b
aseline which will serve as a foundation for future analysis with regard to lung cance
clinical outcomes and health utilization costs.

2) Background

2.1) Lung Cancer Epidemiology

In 2002 there were an estimated 66,200 cancer related deaths in C
anada with a predicted overall case fatality ratio of 0.48. Lung cancer is the lea
ding single cause of cancer mortality and accounted for an estimated 28% (n=18,400
) of all cancer deaths in 2002. Lung cancer has a case fatality ratio of 0.88, second onl
y to pancreatic cancer at 0.99 <1>. It should also be noted that lung cancer is t
ıe leading cause of cancer death worldwide<2>.

Cancer is the leading cause of potential years of life lost (PYLL)
with cardiovascular diseases being second. In 1998 lung cancer accounted for 27% o
f all cancer related PYLL. <1>

Lung cancer incidence rates are second only to prostate cancer i
ı men and breast cancer in women. Although current lung cancer incidence rates
are higher in men versus women the trend over time has been one of rising incide
ıce rates in women and declining incidence rates in men. These temporal trends co
relate with historic smoking rates with a lag period of approximately 15 to 20 year
. <1>

There is a general geographic East to West pattern of lung cancer incidence rates with higher rates being experienced in the East. The 2002 estimated Canadian age standardized lung cancer incidence rates (per 100,000) are 74 and 47, for men and women, respectively. The Alberta lung cancer incidence rates are 64 and 45, for men and women, respectively. <1>

Improvements in lung cancer survival rates have been marginal in the last two decades <3 , 4>. For example, based on the National Cancer Institute (NCI) Surveillance Epidemiology and End Results (SEER) data , the 5 year lung cancer survival rates remained relatively constant between the periods of 1974-76 and 1983-90 being , 12.3% and 13.4%, respectively <5>. These figures are not dissimilar to reported Canadian or Alberta five year age standardized relative survival rates of 13% and 10%, respectively (data based on diagnosis in 1992) <6>.

However, during the latter half of the 1990's there have been substantial advances in the diagnosis, staging and treatment of lung cancer. Such advances require assessment, relative to current clinical and economic data, to investigate both the impact on clinical outcomes and cost-effectiveness. As will be discussed in detail later, our data and the literature demonstrate that lung cancer survival rates improve significantly with detection at early stages of disease. In addition, quality of life may improve with increasing accuracy of staging in that unnecessary procedures may be averted or potentially beneficial procedures may be realized. Therefore, assessing the accuracy of technological advancements in relation to lung cancer detection and staging is essential.

2.2) Lung Cancer Diagnosis

The following provides a brief review of recent technological advances in the diagnosis and staging of lung cancer with respect to computed tomography (CT) and positron emission tomography (PET). It is not meant to be a comprehensive review but provide a background context for the remainder of the thesis.

Prior to the advent of CT, chest imaging was limited to plain film radiography, planar tomography or fluoroscopy. The first CT, which was limited to head scans, was introduced in 1972. Whole body CT imaging began around 1976. Since then there have been remarkable advances in the resolution and speed of CT scans. <7> .

2.2.1) CT Lung Cancer Staging

CT is the current standard diagnostic imaging technique used for staging and investigation of lung cancer. It is used in concert with invasive procedures such as bronchoscopy, mediastinoscopy, video assisted lung thoracoscopy, CT guided lung biopsy and open lung biopsy <8 - 11>. The lead role of CT imaging in the diagnosis and staging of lung cancer is being challenged by PET imaging which appears to provide a higher diagnostic yield. PET imaging will be discussed later in the introduction.

Because of the lack of success of sputum cytology and chest x-ray screening programs <12>, there is significant interest in CT lung cancer screening.

2.2.2) CT Lung Cancer Screening

For example, Nawa et al <13 > recently published the results of low dose CT screening in a recent (1998 to 2000) Japanese occupational cohort (aged 50 to 69) of

which 7,959 had baseline CT screening scans and 5,568 had repeat CT screening at one year. The majority (i.e. 77%) of the cohort were either current or former smokers. Suspicious pulmonary nodules were followed as per a prescribed algorithm starting with a diagnostic CT scan. If the nodule was <11 mm, sequential repeat scans were done to assess growth. If the nodule was ≥ 11 mm then an invasive test was recommended.

Baseline screening identified 2,865 non-calcified solitary pulmonary nodules in 2,099 patients (26% of those screened). The baseline prevalence of lung cancer was 0.44% (36 patients) with 86% being stage I. Of the 5,568 individuals who underwent repeat screening at one year an additional 4 lung cancer cases were detected resulting in a one year incident lung cancer rate of 0.07% with all being at stage Ia. Overall, ten false positive cases were reported which constitutes a 21% false positive rate for biopsied lesions. These false positive cases are important as related to potential procedure related morbidity and mortality. As will be discussed later, PET imaging may reduce this false positive rate.

Interestingly, Nawa et al <13 > also reported that women had overall increased rates of lung cancer and in the 12 cases of lung cancer in women none of the women were smokers or had known occupational risk factors. The authors state that no information was available on passive or "second-hand" smoke exposure. This raises the issue of who should be targeted for CT lung cancer screening.

Henschke et al <14> published the results of a prospective trial which enrolled 1,000 asymptomatic individuals, 60 years or older (median age 67), who had at least a 10 pack year smoking history (median 45 pack years). Suspicious pulmonary nodules were further assessed by a diagnostic CT scan and thereafter managed through a pre-hoc protocol relative to nodule size. The prevalence of non-calcified nodules and malignancy was 23% and 2.7%, respectively. The prevalence of malignancy in Henschke et al's population is over 6 times higher than what Nawa et al <13 >

reported indicating that Henschke et al's <14> population may have been at higher risk (e.g. older and confirmed 10 pack years of smoking).

Henschke et al <14> reported that of the thirty three lesions biopsied only 4 (12%) were non-malignant or false positive. This is lower than Nawa et al's <13> false positive rate of 21% and in keeping with a higher pre-test probability of having lung cancer.

Similar to Nawa et al's <13> study, Henschke et al <14> reported that a majority of detected malignancies, i.e. 85%, were stage I.

In addition, work on the cost effectiveness of lung cancer screening with CT has recently been published by Chirkos et al <15>. The incremental cost per year of life gained ranged from $33,557 to $90,022 (US$) corresponding to pre-test probabilities of localized disease of 70% to 30%, respectively.

The use of low dose CT scans for lung cancer screening is still controversial and the National Cancer Institute is currently conducting a large trial (i.e. the Lung Cancer Screening Study) where individuals are randomized to either base line and one year chest radiographs or low dose CT scans <16>.

In screening programs lead and length time bias have to be considered in addition to the overall goal of doing more good than harm <17-19>.

Lead time bias is detecting the disease earlier in its natural history while not changing the date of death. This gives the false impression of extending survival or extending time to death. To help control for lead time bias changes in mortality rates are analyzed in addition to survival rates. That is, with lead time bias there will be no change in mortality rates but just apparent survival times.

Length time bias relates to an increased rate of detection of slower growing or more indolent cancers which will bias the results to apparent, but false, increased survival. One could argue that stage I NSCLC may be less aggressive and may, in fact, be indolent. Dominioni et al <20> provide good arguments against this by demonstrating that: there are no histology biases between screened or incidentally detected stage I NSCLC; tumor doubling times for stage I cancer are significantly shorter than for benign lesions; and 5 year survival times for surgically resected stage I NSCLC (~ 80%) are significantly better than for unresected disease (≤ 10%).

One may ask, is 5 year survival a reasonable end point for which to declare a cure? Why is there only 80% survival at 5 years for stage I NSCLC? Dominioni et al <20> argue that staging is not perfect and those who survive to 5 years without recurrence have a 94% chance to survive to 10 years. They also argue that for stage I NSCLC, recurrence rates plateau at about 5 years making this a reasonable "cure" endpoint.

Thus, it appears that CT screening may provide us with an opportunity to detect lung cancer at an earlier stage and potentially reduce lung cancer mortality. Screening programs have to balance the benefit of screen positive cancers from the harm related to the investigation of false positives. As will be discussed next PET imaging may have a role in reducing the potentially harmful effects of lung cancer screening by reducing false positive rates.

2.2.3) PET Imaging in Lung Cancer

Positron emission tomography (PET) with a radio-labeled sugar (18-fluorodeoxyglucose or FDG) has been around since the late 1950's <21> but has not played a significant role in oncology imaging until recently. The use of FDG PET imaging has experienced rapid expansion in both Europe and the United States of America (US) and is slowly being introduced in Canada <22>. Expansion in the US has largely been driven by public health reimbursement policies of the former Health

Care Finance Administration (HCFA), which was the precursor to the current Centers for Medicare and Medicaid Services (CMS). In 1998 the HCFA approved funding for FDG PET imaging for solitary pulmonary nodules and non-small cell lung cancer (NSCLC) staging<23>.

There is growing evidence that 18-fluorodeoxyglucose positron emission tomography (FDG PET) imaging contributes to further improvements in the accuracy of lung cancer staging <24-27> which should further improve patient selection, especially with regard to surgical interventions.

The summary sensitivity, specificity and accuracy estimates for FDG PET imaging for the diagnosis of lung cancer are 96%, 73% and 90%, respectively and the same figures for staging lung cancer are 98%, 92%, and 96%. This is compared to summary sensitivity, specificity and accuracy estimates for CT staging of lung cancer of 72%, 95% and 85%, respectively <24>.

The important outcome of the increased diagnostic accuracy of FDG PET, relative to CT imaging alone, is improved patient management. Pietermann et al <25> compared preoperative staging with FDG PET and CT imaging in 102 individuals and reported that FDG PET changed staging in 62 individuals (61%) with the stage being lowered in 20 patients and raised in 42. These results would imply that patient management may be significantly altered when FDG PET imaging is utilized. That is, those individuals "up-staged" beyond stage IIIa NSCLC could be spared non-beneficial or futile major thoracic surgery and those "down-staged" to below stage IIIb NSCLC may benefit from surgery.

In another example, Tinteren et al <28> randomized patients with suspected potentially resectable NSCLC, who had been clinically but not surgically staged, into conventional work up (n=96) or conventional work up plus FDG PET imaging (n=92). They reported that the addition of PET prevented unnecessary or futile surgery (i.e. thoracotomies) in 20% of patients with suspected NSCLC. This is similar

to Vesselle et al's <29> prospective study which reported that FDG PET detected unsuspected advanced disease in 30 of 142 (21%) patients who were thought to have resectable NSCLC.

In another prospective study (n=153) Hicks et al reported that PET down-staged 10% and up-staged 33% of cases <26>.

To this end FDG PET imaging is advancing the accuracy of the diagnosis and staging of lung cancer and the inclusion of PET imaging to assist in the management of lung cancer may become the standard of care.

2.3) Lung Cancer Therapy

At this point it would be logical to ask: Given these advances in the diagnosis and staging lung cancer, have there been any advances in lung cancer therapy?

It appears that surgical techniques for NSCLC have remained unchanged in the last few decades. However, largely due to advances in diagnostic investigations and pre-surgical risk assessment, there have been significant advances in patient selection and stratification. As discussed by Pearson <30> 40% of cases were found to have unresectable disease at thoracotomy in 1960. It would now be very unusual to be surprised by unexpected macro-disease during thoracotomy. In fact, with FDG PET imaging we are entering the realm of pre-operatively detecting otherwise occult disease.

Pearson also attributes the significant historical drop in overall peri-operative mortality rates, from about 10% in 1960 to about 3% in 1985, to better pre-operative medical assessment and patient selection <30>.

There have also been advances in chemotherapy and radiotherapy for non-surgically resectable NSCLC or as adjunctive therapy in surgically resectable NSCLC.

Chemotherapy is the mainstay of therapy for SCLC with radiotherapy having a minor role <10,11>. A full discussion on such advances are beyond the scope of this thesis and only a brief discussion, with a focus on NSCLC, will ensue.

Prior to the 1990's, chemotherapy did not result in demonstrable improvements in survival for NSCLC <31>. Since the 1990's a number of new chemotherapeutic agents, such as cisplatin and paclitaxel, have demonstrated improved quality of life and improved survival, albeit the latter being minimal in advanced disease <31>. Research is also being conducted on combined chemotherapy - radiotherapy treatment protocols <32>.

For NSCLC, the National Cancer Institute comments that chemotherapy and radiotherapy contribute most by reducing disease-related symptoms <10> .

In light of the recent technological advances outlined above it is time to move on from the depressing statement that; "lung cancer mortality rates have not changed significantly in the past decade". It is time to be optimistic about the potential positive impact that new technologies and screening programs may have on the natural history of lung cancer.

3) Methodology:

A literature search was conducted (literature cited from 1966 to July 2002) initially utilizing Grateful Med®, and then Pub Med® (National Library of Medicine) and Ovid Medline (Ovid Technologies Inc.). Grateful Med® was replaced by Pub Med® by the National Library of Medicine during the course of this research. The literature search included a general review of the epidemiology, screening, diagnosis, and management/treatment of lung cancer. Additional searches were conducted for specific lung cancer diagnostic imaging modalities (e.g. CT, MRI, PET) as well as for the economics of lung cancer. Elements of the literature search strategy can be found in Appendix A.

The study cohort was identified through the Alberta Cancer Registry[1] (ACR) and included 1998 incident cases of primary bronchogenic lung cancer as classified by the International Classification of Diseases - Oncology (ICD-O). The search was limited to cases from the Edmonton Cross Cancer Institute's (CCI) catchment area (i.e. essentially the Northern half of the Province of AB).

The Northern half of the Province was chosen to maximize the likelihood of clinical charts being available at the Cross Cancer Institute (CCI).

A 1998 cohort was used as this was the most recent year for which complete data were available. There were only minor variations per year in the number of Alberta Cancer Registry identified lung cancer cases ascribed to the Northern half of Alberta between 1995 to 1998.

Charts and microfiches were reviewed by an experienced health care worker. Data were transcribed onto paper data abstraction forms (see Appendix B) which were developed through iterative consultation with individuals who have specific content

[1] The numbers are provisional as some cases (or deaths) may be registered in subsequent years. Methods of coding of cancers on the Alberta Cancer Registry have varied through the years. Therefore caution should be exercised when comparing data to those of previous years.

and methodological knowledge relative to this research. The first 15 abstracted charts were comprehensively reviewed as a validation exercise and no significant deviations were demonstrated. In addition, if there was uncertainty related to any data variable, the chart was set aside for review. Most of these reviews were in relation to assessing the assigned stage and chemotherapy protocols.

An electronic database emulating the data abstraction form was constructed using FileMaker Pro 5® Software. Table 1 outlines the data variables stratified by the following categories: demographics, clinical information and health service interventions.

The diagnosis date is defined as the date of most definitive diagnosis as per the ACR Coding Manual. In broad categories histopathology is the most definitive diagnosis followed by cytology, diagnostic imaging and then clinical impression.

ACR records, which are regularly updated and linked with provincial vital statistics and national mortality data bases, were used to assess survival to two years from the date of diagnosis.

Staging for non-small cell lung carcinoma (NSCLC) was determined as per the 1997 revised TNM classification for staging lung cancer <33>. If a separate surgical stage was recorded then the surgical stage was utilized, otherwise the clinical stage was entered. A summary of the 1997 revised classification can be found in Appendix C.

Small cell lung carcinoma (SCLC) was recorded as limited or extensive based on the impression recorded by the clinician at the initial attendance at the CCI.

Urban versus rural residence was determined as per Canada Post definitions using full postal codes (Canada Post - Canada Postal Guide, October 2001).

For the survival analysis, radiotherapy and chemotherapy were defined as having at least one external beam radiotherapy or chemotherapy treatment/session in relation to the patient's lung cancer. Surgery included open lung biopsy, wedge resection, segmental resection, lobectomy, and pneumonectomy. Mediastinoscopy included all utilized techniques in this cohort (i.e. routine, anterior and extended).

SPSS® Base 10.0 software was used for statistical analysis. Where appropriate, X^2, Student's t test and Cox's proportional regression analyses were used. Statistical significant is declared at $p < 0.05$ (two tailed where applicable). Confidence intervals are reported (95%) when appropriate.

A direct method was used <34> for the calculation of age standardized primary lung cancer incidence rates utilizing the 1991 Canadian standard population as published in the National Cancer Institute of Canada, Canadian Cancer Statistics, 1998 monograph.

For the survival analysis, a Cox's proportional regression survival analysis was used. The hazard ratio and its confidence intervals are given. The hazard ratio, for suspect prognostic variables, is mathematically derived from the survival curve and is a measure of the relative risk of not surviving relative to the baseline or reference state of the chosen variable. For example in a dichotomous variable, such as presence or absence of a hypothesized prognostic variable, a hazard ratio of 2 would infer a two times relative risk of dying with the variable being present versus absent. The proportional hazards assumption was tested by generating and inspecting the log-minus-log plots. Events were censored at 2 years from the date of diagnosis.

The univariate Cox regression analysis was conducted on the following variables: patient age at date of diagnosis (exact age as well as by decade), urban/rural residence, gender, smoker (yes or no), number of years smoking, number of pack years smoked, histology (for NSCLC and other cancers), stage , mediastinoscopy, surgery, chemotherapy and radiotherapy. The latter 4 variables were entered as binary yes/no variables. Due to small numbers "other" cancers were not included.

Stratified by NSCLC and SCLC, variables which achieved significance in the univariate analysis were entered in a multivariate Cox's proportional hazards regression model utilizing a forced entry model. Interaction was assessed in NSCLC for mediastinoscopy*surgery, mediastinoscopy*stage, surgery*stage, and chemotherapy*stage, and in SCLC for radiotherapy*stage and chemotherapy*stage. For further details, selected SPSS® Cox regression outputs with explanatory annotations, are illustrated in Appendix D.

This research protocol was granted ethics approval from the Alberta Cancer Board – Research Ethics Committee.

4) Results

4.1 Descriptive Epidemiology

Of the initial 742 individuals identified through the ACR, three cases were excluded as they did not have primary lung cancer diagnoses (i.e. two lymphomas and one lung cancer recurrence). Of the remaining 739 individuals, 128 were listed on the cancer registry but had insufficient clinical information for review (i.e. no charts, no microfiches or no significant clinical entries). Only demographic and tumor histology information could be collected for these 128 individuals. Detailed demographic, clinical and health utilization data were collected for the remaining 611 individuals (83% of the 739 incident primary lung cancer cases).

The age standardized primary lung cancer incidence rates (per 100,000) for males, females and gender combined were 62, 42 and 50, respectively (n=739).

Unless otherwise specified all further analysis will be based on the 611 primary lung cancer cases for which more detailed clinical information was available.

The mean age at time of diagnosis was 66.5 years (SD=11, range 14-93). On average, males were slightly older than females (67.6 versus 65.1, p=0.005). Males accounted for 55% of the cohort. The majority of cases (79%) had urban residences with the remainder having rural residences. The urban-rural split, as determined from the patient's residential postal code (Canada Post Guide), concurs with the published figure of 79% urban for the general Alberta population as per 1996 Canadian Census data (Statistics Canada – Cat. No. 92-351-XPE).

Table 2 illustrates the frequency of histological diagnosis. Overall, adenocarcinoma and squamous cell carcinoma were the most frequent NSCLC histologies. There were no significant differences in the distribution of the broad categories of NSCLC, SCLC and "other" lung cancers by gender.

Amongst NSCLC the proportion of adenocarcinoma was significantly higher in females (60% females and 51% males, χ^2test p=0.04) with the proportion of squamous cell carcinoma being higher in males (38% males and 24% females, χ^2test p=0.003). Other NSCLC histologies demonstrated no significant differences in distribution by gender.

There were no significant differences in the distribution of histologies by urban versus rural residence or by stage of disease.

Smoking "yes/no" data was collected in 93% of the cohort. The vast majority, that is 92%, were declared smokers. Amongst smokers there was a mean of 40 years (SD 12) of smoking per individual (data available for 67% of declared smokers) and a mean of 44 pack years (SD 15) of smoking (data available for 39% of declared smokers). There was a significantly higher proportion of smokers with squamous (n=132/136, 97%,) and small cell (n=96/98, 98%) carcinomas versus smokers with adenocarcinoma (n=204/234, 87%), with p=0.002 for both comparisons.

The frequency of presenting clinical stages and survival to two years is illustrated in Table 3. Staging information was available for 91% (411/452) of NSCLC, 97% (102/105) of SCLC and 74% (40/54) of "other" lung cancers. In 38 cases both a clinical and surgical stage were recorded with disagreements in only three instances (surgical stage lower than clinical stage in two cases and higher in one). For these three cases the surgical stage was used.

4.2) Frequency and Type of Health Care Interventions

Table 4 describes the frequency of various interventions by cancer type and presenting stage. Only cases with known stages were included and "other" cancers were not included due to small numbers. For NSCLC there are general trends of increased proportions of thoracic surgeries in lower stages and of increased chemotherapy and radiotherapy interventions in higher stages. Mediastinoscopy rates were lower than expected and this may be related to failure to capture these events. As expected chemotherapy and radiotherapy rates were high for both limited and extensive SCLC.

Table 5 provides details of the type of surgical interventions for NSCLC by stage. Proportionately more aggressive surgery is observed in lower stages. For example, the proportion of any form of resection (wedge, segment, lobe or lung) goes from 71% for stages I through IIIa combined, to 3% for stages IIIb and IV combined.

4.3) Survival Analysis

Information on survival to two years from the date of diagnosis data was available for all 611 individuals. Although there is reasonable survival to two years for stage I or II NSCLC (i.e.,83% and 63% respectively),only a minority of individuals (i.e. 21%) presented in these early stages. There is a rapid decline in survival to two years by increasing stage for NSCLC and poor survival in SCLC irrespective of stage. The overall survival for "other" lung cancers is worse than for NSCLC.

Unadjusted survival curves, stratified by stage, for NSCLC and SCLC, are illustrated in Figures 1 and 2, respectively.

For NSCLC the univariate Cox regression survival analysis demonstrated that the following were associated with a significant survival advantage for up to two years from the date of diagnosis: female gender; lower stages at presentation (reference stage I); and having mediastinoscopy, surgery, radiotherapy or chemotherapy. For SCLC, younger age, fewer pack years of smoking, limited stage, and having radiotherapy or chemotherapy were all associated with significant survival advantage for up to two years from the date of diagnosis. Table 6 illustrates the results of the univariate analysis.

Variables which achieved significance in the univariate model were entered in a forced entry multivariate Cox's proportional hazards regression model. For NSCLC only stage, surgery, and chemotherapy remained significant. For SCLC only stage and chemotherapy remained significant. No significant interaction were detected with respect to: NSCLC - mediastinoscopy*surgery, mediastinoscopy*stage, surgery*stage, and chemotherapy*stage, and in SCLC - radiotherapy*stage and chemotherapy*stage. Table 7 provides the results of the multivariate analysis.

It is generally held that major thoracic surgery does not infer a survival benefit for NSCLC cased beyond stage IIIa <10>. As illustrated in Table 6, it is interesting to note that 12% and 5% of NSCLC stage IIIb and IV patients, respectively, had some form of thoracic surgery. A separate survival analysis was performed including only NSCLC cases above stage IIIa (n=270). Thoracic surgery, chemotherapy, and radiotherapy were entered as categorical variables. As is demonstrated in Table 8 both thoracic surgery and chemotherapy were significantly associated with improved survival to two years from the date of diagnosis. Radiotherapy was not significantly associated survival. the fact that over 80% of NSCLC patients in stages IIIb and IV received radiotherapy may reduce the power of the analysis to reach statistical significance.

5) Discussion

NSCLC adenocarcinoma is the most frequent histology at 55% followed by squamous cell carcinoma (32%), large cell carcinoma (12%) and bronchoalveolar cell carcinoma (2%). This correlates to the North American literature <2, 35, 36> which also demonstrates a preponderance of adenocarcinoma over squamous cell carcinoma. It should be noted that the European literature demonstrates the converse, that is, a preponderance of squamous cell carcinoma over adenocarcinoma <35>. The reason for the difference is not fully understood. Charloux et al <35> state that these differences may be real or due to differential bias including: detection bias, case selection bias or pathological classification bias.

Previously published Canadian data <37>, based on a 1984 Alberta cohort, reported 26%, 15%, 22%, and 37% proportions for stages I, II, III and IV lung cancer, respectively. As illustrated in table 3, our research demonstrated 15%, 6%, 33% and 37%, proportions for stages I, II, III, and IV, respectively, demonstrating an apparent increase in the proportion of higher stages. One reason for this apparent difference may be due to different proportions of unstaged cases. Only 9% (41 out of 452) of our NSCLC cases were of an unspecified stage whereas Gentleman et. al <37> reported 41% (283 of 683) being unstaged. Furthermore, imputed stages were not assigned in our 9% of unspecified stage data whereas Gentleman et. al <37> did utilize imputation methods which resulted in a reduction of stage IV disease and a corresponding increase of lower stages. Other reasons for the apparent difference in distribution of stages may be differences in data collection methodology or changes in methods for assigning stage. For example, Gentleman et. al <37> publication was prior to the 1996 Revised International System for Staging Lung Cancer <33>. It would seem unlikely that the differences are due to a trend of diagnosis at a later stage through time (i.e. 1984 to 1998).

As stage was assigned based on investigations surrounding the ACR's defined date of diagnosis, no significant staging bias exists with respect to the interval between

diagnosis and attendance at the CCI. Patients, on average, were assessed at the CCI within 23 days of diagnosis (95% CI 15 to 30 days) as is illustrated in Figure 3. Although this research did not specifically address the full continuum of wait times between symptoms and diagnosis it is comforting to note that once a diagnosis was made patients were assessed relatively shortly thereafter at the CCI.

As expected, for those who had surgery, the 5% trimmed mean (utilized to address extreme outliers) interval between surgery and diagnosis date was only 4.2 days with a very tight range around the median of 0 days. This is demonstrated in Figure 4.

Gentleman et. al <37> also reported that only 27% of their 1984 cohort were female (SCLC and NSCLC) which is significantly different from our results of 45% being female. This difference is thought to be due to the fact that lung cancer incidence rates have been rising faster in women versus men for the last few decades, most likely due to different historical gender specific smoking rates. Our findings, with respect to proportions of lung cancer cases by gender, generally agrees with the 1998 Canadian Cancer Statistics figures for Alberta (i.e. 42% female) <38>.

In another Canadian retrospective cohort based study (169 patients diagnosed with NSCLC between 1988-90) <39> Ouelette et al reported proportions by stages (female/male) of 25/26, 2/6, 20/34, 6/7 and 25/19 (%/%) for stages I, II, IIIa, IIIb, and IV, respectively. Their data has proportionately more lower stage cases than our results. The differences may be due to different study populations. Our data were based on a Cancer Registry population while those reported by Ouelette et al were based on retrospective cohort (consecutive cases) of individuals attending to a "University Hospital".

Compared to a large North American lung cancer cohort (n=5230) <33> population, our data demonstrated significantly longer 2 year survival rates for stages I, II and all stages combined with significance almost being achieved for stage IV (p=0.06). There was no significant difference for stage III cancers.

Compared to a surgically staged cohort (n=1910) published in the same paper <33>, our findings do not differ significantly. One possible reason for these differences is that Mountain et al's <33> clinically staged cohort included small cell carcinoma (n=642 or 11.9% of the cohort) and their surgically staged cohort did not. We demonstrated that SCLC has a generally poorer prognosis than NSCLC. This may account for the difference demonstrated between our findings and Mountain et al's clinically staged cohort and agreement with Mountain et al's surgically staged cohort. This is illustrated in Table 8.

Fry et al <40> also reported survival by stage in a large (n=713,043) American lung cancer (NSCLC and SCLC combined) cohort diagnosed between 1985–95. The overall survival by stage was 59%, 41%, 24%, 13%, and 5% for stages I, II, IIIa, IIIb, and IV, respectively, which is similar to Mountain et al's <33> clinically staged cohort.

The relatively high 2 year survival of patients with stage I NSCLC (i.e. 83%) in our cohort is in agreement with a recent review by Dominioni et al <20>. This supports the benefit of early diagnosis. Dominioni et al go further to argue that the relatively high 2 year survival rate supports targeted screening of high risk individuals (e.g. smokers).

One of the limitations of multivariate analysis is that significance may not be achieved for variables which have a very skewed distribution. For example 92% of the cohort declared being smokers at some point in their life leaving only 8% non-smokers. There may have been an insufficient number of non-smokers to statistically assess the impact of smoking or non-smoking on survival. In addition, variables with a relatively low frequency or a large number of missing values may also not have sufficient power to achieve statistical significance, especially in the final multivariate survival model. For example, only 18% of NSCLC cases had mediastinoscopy which may have been too few cases to demonstrate a significant effect on survival.

There were 129 individuals identified on the ACR with insufficient information for full analysis. The majority of these cases never attended at the CCI or had very little information available in CCI charts/microfiches. They either went to an alternate Alberta Cancer Centre or never presented to any Alberta Cancer Centre. It is possible that some may have only sought community based palliative care and some may have only received curative surgery.

However, by utilizing the ACB's Axon electronic database, basic demographics and survival data were available for these 128 individuals. With comparisons to our study cohort (n=611) the mean age of this group was older at 72.2 years (P<0.0001), 59% were male (NS), 88% were urban (NS) and 22% survived to two years from the date of diagnosis (NS). It is reassuring to note that these 128 individuals experienced a similar overall survival rate and were similar with regards to gender and urban/rural composition.

Lung cancer is a preventable disease. It has been well established that smoking accounts for 80% to 90% of the population attributable risk for primary lung cancer <41> and that the incidence of primary lung cancer mimics that of smoking rates with a latent or lag period of 15 to 20 years <42>. Given this it is not surprising that over 90% of our study cohort smoked at some point in time.

This research describes the epidemiology and survival experience of a relatively large 1998 Canadian cohort diagnosed with primary lung cancer. Also described is the burden of lung cancer on Canadians with respect to morbidity and mortality.

Given the recent evolution in methods to stage and manage lung cancer this is timely research which provides a Canadian baseline for which to assess new or evolving diagnostic technologies or interventions, including lung cancer screening programs. This research will also assist in addressing future research related to assessing lung cancer clinical practice patterns (e.g. does current practice pattern, including wait

times, reflect established standard of care guidelines?), economic (e.g. what is the cost of the diagnosis and management of lung cancer?) and cost effectiveness (e.g. what is the cost effectiveness of adding PET imaging to the staging algorithm for lung cancer?).

Figure

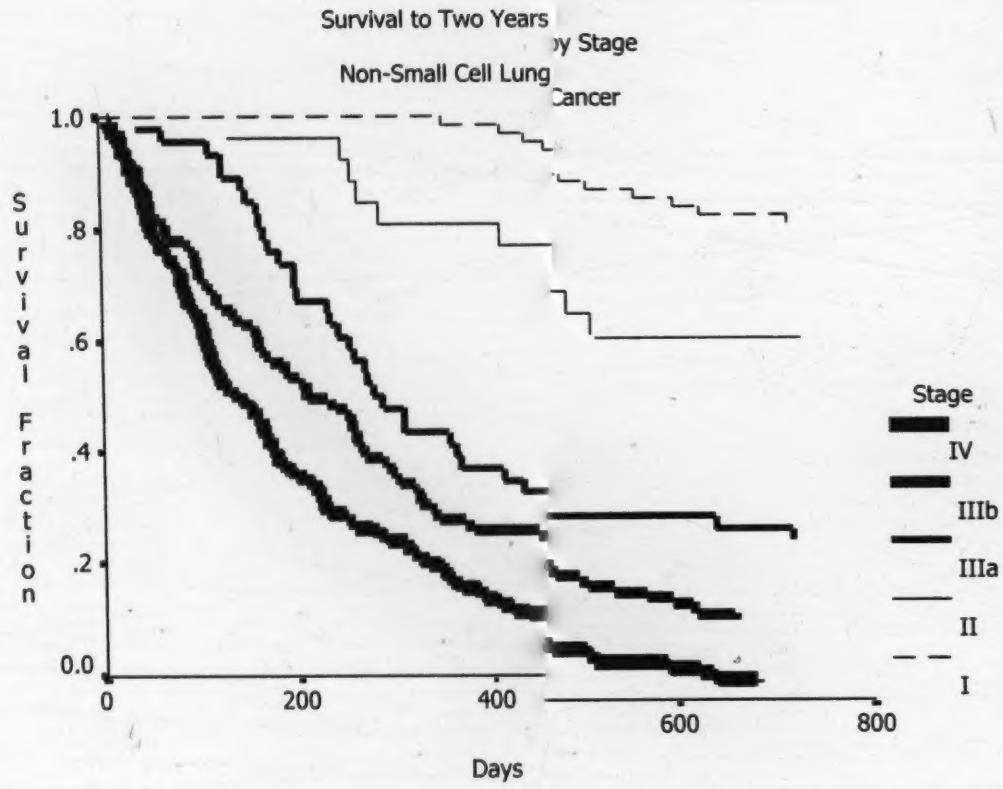
Survival to Two Years
Non-Small Cell Lung Cancer
Survival Fraction
1.0
.8
.6
.4
.2
0.0
0
200
400
600
800
Days
Stage
IV
IIIb
IIIa
II
I

Figure 2

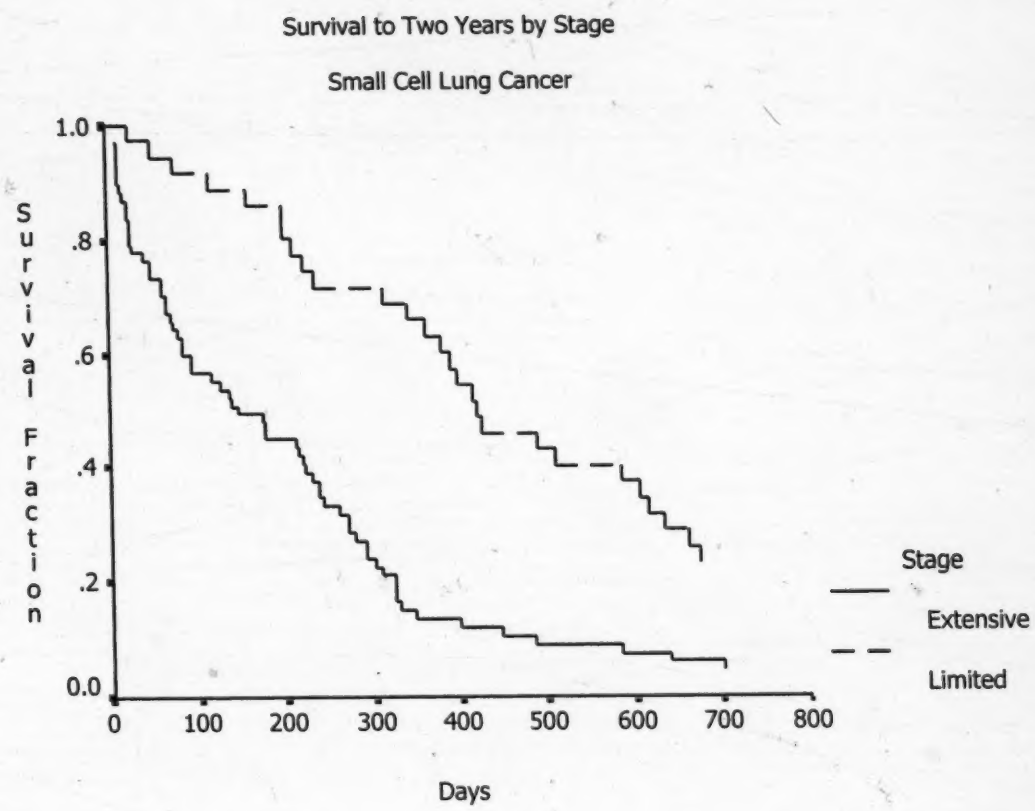
Survival to Two Years by Stage
Small Cell Lung Cancer
Survival Fraction
1.0
.8
.6
.4
.2
0.0
0
100
200
300
400
500
600
700
800
Days
Stage
Extensive
Limited

Figure 3

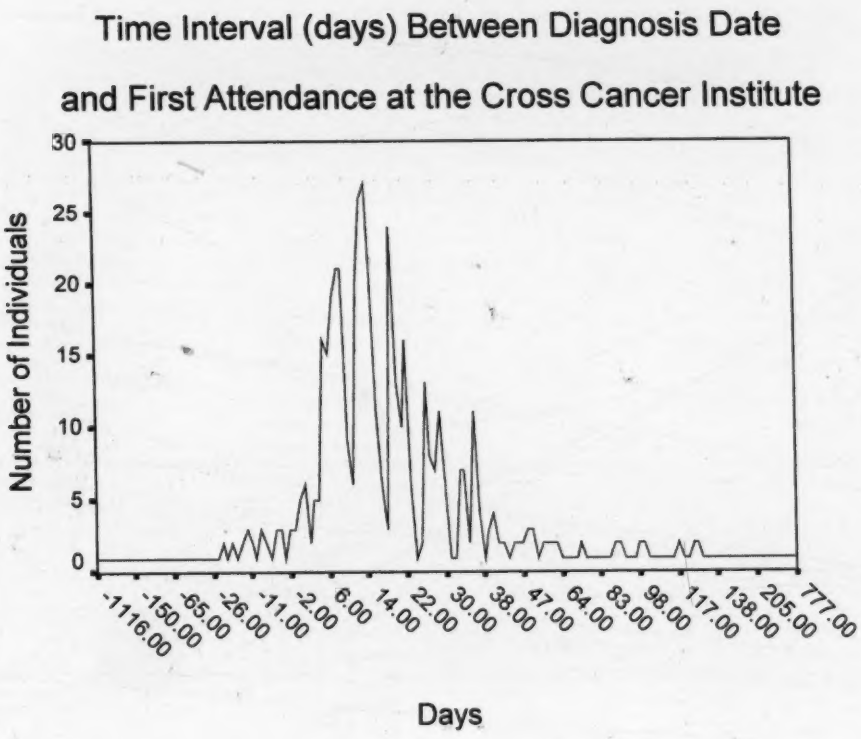
Time Interval (days) Between Diagnosis Date
and First Attendance at the Cross Cancer Institute
Number of Individuals
30
25
20
15
10
5
0
-1116.00
-150.00
-65.00
-26.00
-11.00
-2.00
6.00
14.00
22.00
30.00
38.00
47.00
64.00
83.00
98.00
117.00
138.00
205.00
777.00
Days

Figure 4

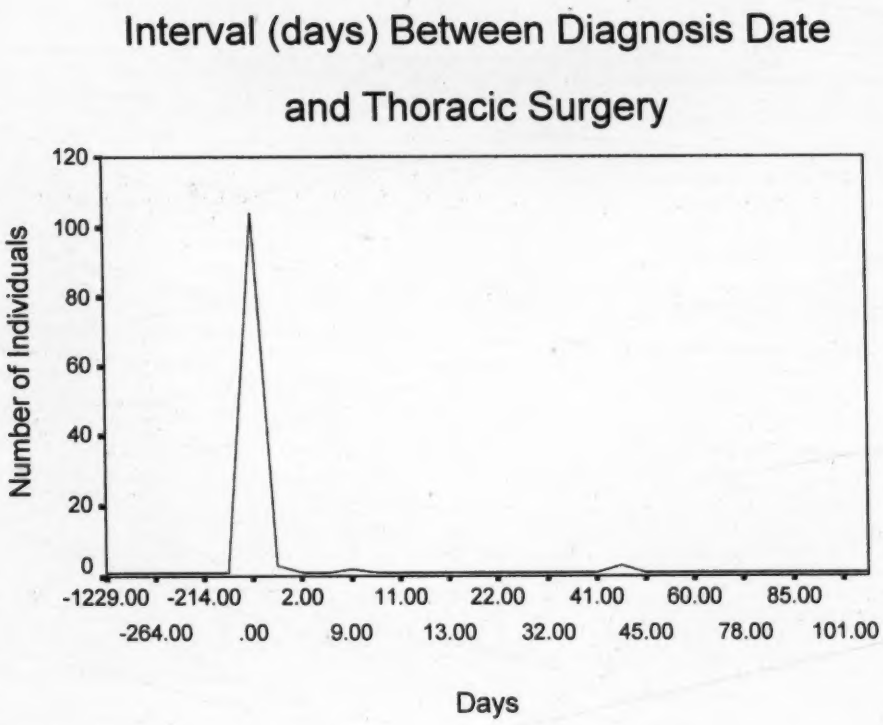
Interval (days) Between Diagnosis Date and Thoracic Surgery
Number of Individuals
120
100
80
60
40
20
0
-1229.00
-264.00
-214.00
.00
2.00
9.00
11.00
13.00
22.00
32.00
41.00
45.00
60.00
78.00
85.00
101.00
Days

Table 1

An Overview of Information Collected

Variable Category	Information Collected
Demographics	unique identifiers date of birth gender postal code
Clinical Information	date of diagnosis smoking history histology clinical staging surgical staging concurrent primary concurrent medical conditions survival to two years post date of diagnosis
Health Service Interventions	health care facility where service was rendered health care consultations: physician, allied health professionals diagnostic imaging: radiography, CT, MRI, ultrasound, nuclear medicine diagnostic laboratory tests: chemistry, hematology, microbiology, urinalysis, immunology, cytology, histology, pulmonary function, arterial blood gasses, ECG, cardiac stress testing therapy/procedures: surgery, endoscopy, chemotherapy, radiation therapy, blood product transfusions, oxygen therapy hospital admissions (number of days)

Table 2

Frequency of Histological Diagnoses

Histology	Number (%)
Adenocarcinoma	250 (41)
Squamous Cell Carcinoma	143 (23)
Large cell Carcinoma	53 (9)
Bronchoalveolar	6 (1)
Mucoepidermoid	1(<1)
Carcinoid	7 (1)
Small Cell	105 (17)
Unspecified Carcinoma	39 (6)
Unspecified Cancer	7 (1)
NSCLC Total*	452 (74)
SCLC Total*	105 (17)
Other Total*	54 (9)
TOTAL	611 (100)

* NSCLC = non small cell cancer includes: adenocarcinoma, squamous cell, large cell and bronchoalveolar carcinomas; SCLC= small cell lung cancer; Other includes mucoepidermoid, carcinoid, unspecified carcinoma and unspecified cancer

Table 3

Frequency of Stage at Presentation and Percent Survival to Two Years from Date of Diagnosis

Cancer Type and Stage	n (%)	% Survival
Non-Small Cell Carcinoma*		
I	68 (15)	83
II	27 (6)	63
IIIa	46 (10)	28
IIIb	105 (23)	14
IV	165 (37)	3
[I-IV]	[411 (91)]	[26]
Unspecified stage	41 (9)	17
All	452 (100)	24
Small Cell Carcinoma*		
Limited	35 (33)	22
Extensive	67 (64)	4
[Limited & Extensive]	[102 (97)]	[11]
Unspecified stage	3 (3)	0
All	105 (100)	10
Other*		
	2 (4)	100
I	2 (4)	50
II	3 (6)	33
IIIa	13 (24)	15
IIIb	21 (39)	0
IV	[40 (74)]	[13]
[I-IV]	14 (26)	15
Unspecified stage		
All	54 (100)	13
Overall	611 (100)	22

* NSCLC = non small cell cancer includes: adenocarcinoma, squamous cell, large cell and bronchoalveolar carcinomas; SCLC= small cell lung cancer; Other includes mucoepidermoid, carcinoid, unspecified carcinoma and unspecified cancer

Table 4

Interventions Stratified by Type of Lung Cancer and Presenting Stage

Cancer Type and Presenting Stage (n)	Med* %	Sx* %	C	hemo* %	RT* %
NSCL*					
I (68)	18	85		9	26
II (27)	30	85		7	41
IIIa (46)	28	46		15	89
IIIb (105)	24	12		12	81
IV (165)	10	5		18	82
All (411)	18	30		14	71
SCLC*					
Limited (35)	31	3		86	83
Extensive (67)	8	1		64	63
All (102)	16	2		72	70

* Med=mediastinoscopy, Sx=invasive thoracic surgery (include open lung biopsy, wedge resection, segmentectomy, lobectomy and pneumonectomy), C=chemo=chemotherapy, RT= external beam radiotherapy, NSCLC = non small cell cancer includes: adenocarcinoma, squamous cell, large cell and bronchoalveolar carcinomas; SCLC= small cell lung cancer (surgeries included one open lung biopsy and one pneumonectomy)

Table 5

Frequency of Surgical Interventions (n) by Stage for NSCLC

Type of Surgery/Stage	I	II	IIIA	IIIB	IV
Open lung biopsy	0	0	2	6	3
Wedge Resection	4	0	0	1	0
Segmental Resection	1	0	2	0	0
Lobectomy	49	13	9	3	1
Pneumonectomy	4	10	8	0	4
Unspecified	0	0	0	3	0
No Surgery	10	4	25	92	157
Total (% with surgical intervention)	68 (85)	27 (85)	46 (46)	105 (12)	165 (5)

Table 6

Cox Regression Analysis* of Selected Variables

Variable		Type of Cancer†	Hazard Ratio‡	95% CI for Hazard Ratio
Age (years) at Date of Diagnosis		NSCLC	ns	
		SCLC	1.04	1.02 , 1.06
Gender (female reference)		NSCLC	1.3	1.1 , 1.6
		SCLC	ns	
Number of Pack Years smoked		NSCLC	ns	
		SCLC	1.02	1.003 , 1.04
Stage§	I	NSCLC	Reference	
	II		2.7	1.1 , 6.3
	IIIa		7.6	3.9 , 15.1
	IIIb		12.3	6.6 , 23.2
	IV		19.9	10.7 , 37.0
	Limited	SCLC	Reference	
	Extensive		2.8	1.8 , 4.4
Mediastinoscopy‖		NSCLC	0.7	0.5 , 0.9
Surgery‖		NSCLC	0.2	0.1 , 0.3
Radiotherapy‖		NSCLC	2.0	1.6 , 2.6
		SCLC	0.4	0.2 , 0.5
Chemotherapy‖		NSCLC	0.7	0.5 , 0.9
		SCLC	0.2	0.1 , 0.3

* Univariate analysis – survival to two years from the date of diagnosis
†NSCLC = non small cell cancer; SCLC= small cell lung cancer
‡ Hazard Ratio equals Exp(B) in SPSS output and is related to the risk, relative to the baseline or reference condition, of not surviving to two years from the date of diagnosis, CI= 95% confidence intervals for the Hazard Ratio
§ Stage entered as a categorical variable with stage I or limited stage as the reference comparator
‖ mediastinoscopy included all utilized techniques in this cohort (i.e. routine, anterior and extended), surgery included open lung biopsy, wedge resection, segmental resection, lobectomy, or pneumonectomy, radiotherapy and chemotherapy treatments/sessions were related to the patient's lung cancer

Table 7

Multivariate Cox Regression Analysis* of Selected Variables

Variable		Type of Cancer†	Hazard Ratio‡	95% CI for Hazard Ratio
Stage§	I	NSCLC	Reference	
	II		2.7	1.2 , 6.4
	IIIa		6.4	3.1 , 13.2
	IIIb		9.0	4.6 , 17.9
	IV		14.5	7.3 , 29.0
	Limited	SCLC	Reference	
	Extensive		2.2	1.02 , 4.9
Surgery‖		NSCLC	0.5	0.4 , 0.7
Chemotherapy‖		NSCLC	0.5	0.4 , 0.7
		SCLC	0.02	0.002 , 0.1

* forced entry model, survival to two years from the date of diagnosis
†NSCLC = non small cell cancer; SCLC= small cell lung cancer
‡ Hazard Ratio equals Exp(B) in SPSS output and is related to the risk, relative to the baseline or reference condition, of not surviving to two years from the date of diagnosis, CI= 95% confidence intervals for the Hazard Ratio
§ Stage entered as a categorical variable with stage I or limited stage as the reference comparator
‖ surgery included open lung biopsy, wedge resection, segmental resection, lobectomy, or pneumonectomy and chemotherapy treatments/sessions were related to the patient's lung cancer

Table 8
Multivariate Cox Regression Analysis* of Selected Variables
in Stage IIIB and IV NSCLC Patients

Variable	Hazard Ratio‡	95% CI for Hazard Ratio
Surgery‖	0.4	0.2 , 0.8
Chemotherapy‖	0.5	0.4 , 0.8
Radiotherapy‖	0.8	0.6 , 1.1

* forced entry model, survival to two years from the date of diagnosis
†NSCLC = non small cell cancer
‡ Hazard Ratio equals Exp(B) in SPSS output and is related to the risk, relative to the baseline or reference condition, of not surviving to two years from the date of diagnosis, CI= 95% confidence intervals for the Hazard Ratio
‖ surgery included open lung biopsy, wedge resection, segmental resection, lobectomy, or pneumonectomy, radiotherapy and chemotherapy treatments/sessions were related to the patient's lung cancer

Table 9

Survival to Two Years by Stage – A Comparison To the Literature

Stage - NSCLC	Study Data (n=411) %	Clinical Staging <13> (n=5230) %	P‡	Surgical Staging <13> (n=1910) %	P‡
Ia	(30/31) 97	79	0.02	86	NS
Ib	(25/33) 76	54	0.01	76	NS
I*†	(56/68) 83	66	0.002	81	NS
IIa	(7/10) 70	49	NS	70	NS
IIb	(10/16) 63	41	NS	56	NS
II†	(17/27) 66	44	0.05	61	NS
IIIa	(13/46) 28	25	NS	40	NS
IIIb	(15/105) 14	13	NS		
IV	(5/165) 3	6	NS		
Stage I – IV†	(107/411) 26	22	0.05		

* four stage I cancers and one stage II cancer were not subcategorized
†adjusted for differences in distributions of stages between the two cohorts
‡ NS= not significant

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Appendix A

Literature Search
Key Word Search Parameters

Literature Search Strategy

The National Library of Medicine was searched via Grateful Med® or Pub Med® or Ovid Medline (Ovid Technologies Inc.) search strategies, and combinations thereof, are as follows. Initially Grateful Med was used and thereafter Pub Med and Ovid Medline were used predominately.

Query As Sent	Explanation
(notpubref[sb] AND ((((("lung neoplasms"[MeSH Terms] OR lung cancer[Text Word]) OR "carcinoma, bronchogenic"[MeSH Major Topic]) OR "adenocarcinoma" [MeSH Terms]) OR "carcinoma, small cell"[MeSH Major Topic]) OR "lung neoplasms" [MeSH Major Topic]) OR "bronchial neoplasms"[MeSH Major Topic]))	lung cancer *Carcinoma, Bronchogenic Adenocarcinoma *Carcinoma, Small Cell *Lung Neoplasms *Bronchial Neoplasms
(notpubref[sb] AND ((((("tomography, emission-computed"[MeSH Terms] OR "animals, domestic"[MeSH Terms]) OR PET[Text Word])OR "tomography, emission-computed"[MeSH Major Topic]) OR"tomography, emission-computed, single-photon"[MeSH Major Topic]))	PET *Tomography, Emission-Computed *Tomography, Emission-Computed, Single-Photon
(notpubref[sb]AND(*Economics[All Fields] OR (("economics" [Subheading] OR "economics" [MeSH Terms]) OR economics [Text Word]))))	*Economics economics
(tomography, x-ray computed"[MeSH Terms]) OR CT[Text Word])	CT
("magnetic resonance imaging"[MeSH Terms] OR MRI[Text Word])	MRI
("mass screening"[MeSH Terms]) OR screening[Text Word])	screening

Appendix B

Data Abstraction For[illegible]

LUNG PATIENT SUMMARY SHEET

DEMOGRAPHICS

Last Name: First Name Init. _____ **Sex** □ M □ F

Hospital: **E**_____ Date of: __/__/19__ Date of: __/__/__ **Post**

____ _____ **i.e. (T 6 G)** **I T**

Admitting Number **BIRTH** Month Day Year **DEATH** Month Day Year **Code** _____

_ **i.e. (1 Z 2)**

PHN # Comments:

CLINICAL HISTORY

Date of Diagnosis __/__/19__ **Primary Lung** **Tumor** □ Small Cell □ Adenocarcinoma

Month Day Year **Type** □ Squamous □ Large Cell

Date of Admission __/__/19__ **Concurrent** □ YES Location □ Other ___

Month Day Year **Primary?** Pathology ___

Staging T_____**N**_____**M**_____ **at Admission.** = _____ (stage) Other Concurrent Disease at Admission

Staging T_____**N**_____**M**_____ **at 1st Surgery** = _____ (stage)

Is Patient a smoker? □no □yes. If "Yes", how many packs/day? _____ X How many years? _____ = _____Pack Yr.

Chronological History

Event Date (mm,dd,yyyy)	Event (Procedure)	Location	Details
___ ___ _____			
___ ___ _____			

Appendix C

Source: Adapted from,

National Cancer Institute. Non-small Cell Lung Cancer (PDQ®): Treatment. Last Modified 09/2002. Cited Nov 25/02. Available from: URL http://cancer.gov/cancer_information/cancer_type/lung/

The Revised International Staging System for Lung Cancer

The Revised International System for Staging Lung Cancer was adopted in 1997 by the American Joint Committee on Cancer and the Union Internationale Contre le Cancer.[1]

The American Joint Committee on Cancer (AJCC) has designated staging by TNM classification.[2]

TNM Definitions

Primary tumor (T)

TX: Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

T0: No evidence of primary tumor

Tis: Carcinoma in situ

T1: A tumor that is 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, and without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*

T2: A tumor with any of the following features of size or extent:
More than 3 cm in greatest dimension
Involves the main bronchus, 2 cm or more distal to the carina
Invades the visceral pleura
Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T3: A tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung

T4: A tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion **

*Note: The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1.

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[1] Mountain CF: Revisions in the International System for Staging Lung Cancer. Chest 111(6): 1710-1717, 1997.

[2] Lung. In: American Joint Committee on Cancer: AJCC Cancer Staging Manual. Philadelphia, Pa: Lippincott-Raven Publishers, 5th ed., 1997, pp 127-137.

**Note: Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is nonbloody and is not an exudate. When these elements and clinical judgement dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged as T1, T2, or T3.

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor

N2: Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)

N3: Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant metastasis (M)

MX: Distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis present

Note: M1 includes separate tumor nodule(s) in a different lobe (ipsilateral or contralateral).

Specify sites according to the following notations:

BRA = brain	EYE = eye	HEP = hepatic
LYM = lymph nodes	MAR = bone marrow	OSS = osseous
OTH = other	OVR = ovary	PER = peritoneal
PLE = pleura	PUL = pulmonary	SKI = skin

AJCC stage groupings

Occult carcinoma	TX, N0, M0
Stage 0	Tis, N0, M0
Stage IA	T1, N0, M0
Stage IB	T2, N0, M0
Stage IIA	T1, N1, M0
Stage IIB	T2, N1, M0 , T3, N0, M0
Stage IIIA	T1, N2, M0 , T2, N2, M0 , T3, N1, M0 , T3, N2, M0
Stage IIIB	Any T, N3, M0 , T4, Any N, M0
Stage IV	Any T, Any N, M1

Appendix Ð

Sample Cox Regression Analysis Output With Selected Edited Figures for Assessment of Survival by Stage (categorical variable) for NSCLC

Introduction

Cox regression analysis (Cox) is a form of survival analysis. Survival analysis must be able to handle censored data. Censored data are cases which have not experienced the outcome of interest by the end of the study. The Cox model includes censured cases in the survival. In our research individuals were followed for a period of up to two years from the date of diagnosis and if they were still alive at this point they would be handled as a censured case. A Kaplan-Meier model can also be used for survival analysis with censure data however the Cox approach allows for multivariate analysis whereas the with Kaplan-Meier model does not.

The Cox model uses a hazard function to estimate the risk of the outcome, in our case death, at any particular point or interval in time (i.e. at time *t*). It can be expressed as :

$$h(t)=[h_0(t)]e^{(BX)}$$

where :

$h_0(t)=$ baseline hazard function with the covariate X set to 0

$B =$ the regression coefficient (i.e. change in outcome per change in variable of interest)

$X =$ the state of the covariate, for a binary variable it would be 0 and 1 with 0 being the baseline comparator

$E =$ base of the natural logarithm

It should be noted that the hazard function can be derived from the survival function which is the proportion surviving beyond a specified time (t). For the Cox model the mathematical relationship is:

$$H(t)= - lnS(t)$$

Where:

$H(t)$ = the cumulative hazard function
$S(t)$ = the survival function

One major the strengths of the Cox model is t
relation to the distribution of the survival time
assumption in that the effects of variables on
way of putting this is that the hazard ratio is c
the proportionate hazards assumption. To tes
assumption one can plot the hazard functions
visually inspect a plot of the cumulative haza
the baseline hazard functions are equal and p
thereafter. An alternate approach is to constr
survival function. In a LML plot if the indivi
fashion the proportionate hazards assumptio

at it has very few assumptions in
s. However there is one significant
urvival are constant over time. Another
nstant over time and this is known as
for the proportionate hazards
for the various variables over time and
d function over time and determine if
ogresses in a proportionate fashion
ct a "log-minus-log" (LML) plot of the
ual curves should run in a parallel
has been met.[2]

To illustrate the above selected SPSS output
below.

with annotation (in italics) are provided

Cox Regression

Case Processing Summary

		N	Percent
Cases available in analysis	Event[a]	304	67.3%
	Censored	107	23.7%
	Total	411	90.9%
Cases dropped	Cases with missing values	41	9.1%
	Cases with non-positive time	0	.0%
	Censored cases before the earliest event in a stratum	0	.0%
	Total	41	9.1%
Total		452	100.0%

a. Dependent Variable: days survived to two yrs

Event= death ***number of cases who expe ienced the outcome of interest, in this case***

Censored = the number of cases who did not e perience the outcome of interest by a specific date, in our case by two years from the date of diagnosis, and were handled as censored cases

[2] References Altman DG. Practical Statistics for M edical Research. 1st ed. London, England; Chapman and Hall: 1991, and SPSS Advanced Models 10.0 SPSS Inc. Chicago (IL):1999, Walters SJ,

Cases with missing values = cases with no data for the predictor variable of interest – in this case 41 cases of NSCLC did not have stage information

Categorical Variable Codings[a,b]

		Freqency	(1)	(2)	(3)	(4)
STAGE	1.00	68	.000	.000	.000	.000
	2.00	27	1.000	.000	.000	.000
	3.00	46	.000	1.000	.000	.000
	4.00	105	.000	.000	1.000	.000
	5.00	165	.000	.000	.000	1.000

a. Indicator Parameter Coding

b. Category variable: STAGE (stage 0-4 NSCLC and 0-1 SCLC)

This table identifies the variables entered as categorical and identifies "stage 1.00" as the reference category. Entering variables as categorical is robust as it makes no assumptions about a relationship pattern (e.g. trend) amongst the strata.

Variables in the Equation

	B	SE	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
						Lower	Upper
STAGE			4	.000			
STAGE(1)	.984	.437	1	.024412	2.674	1.1	6.3
STAGE(2)	2.034	.349	1	.000000	7.641	3.9	15.1
STAGE(3)	2.513	.321	1	.000000	12.342	6.6	23.2
STAGE(4)	2.993	.316	1	.000000	19.937	10.7	37.0

Stage =Stage I
Stage(1)=Stage II
Stage(2)=Stage IIIa
Stage(3)=Stage IIIb
Stage(4)= Stage IV

B= the predicted change in log hazard per unit change in the predictor variable.

SE= the standard error for B

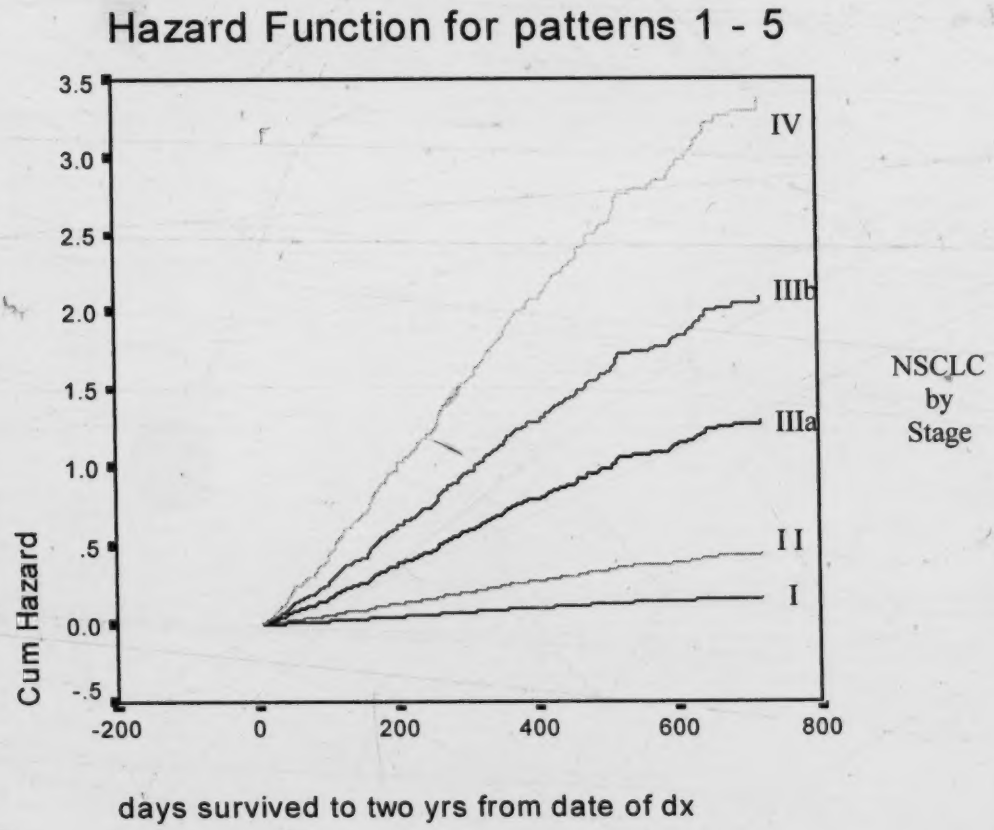
df= degrees of freedom

Sig. = is B significantly different from 0? This is the p value for the Wald statistic

Exp(B)= is the hazard ratio and for dichotomous variables it would express the relative risk for the outcome relative to the baseline (i.e. if gender were the variable and female was the baseline state and the Exp(B) =2 then the outcome would be twice as likely if you where male). If there are multiple levels or strata in the variable then Exp(B) represents the relative change in risk compared to the baseline. For example the increases in risk of death by stage for our data, compared to the baseline state of

Stage I are 1.1 (or 10% increase) for Stage II, 3.9 times for Stage IIIa , 6.6 times for stage IIIb and 10.7 times for Stage IV.

To test for the assumption of proportional hazards, that is that the ratio between the baseline hazard and the model with the predictor variable of interest is relatively constant, on can do two things. The first is to plot the cumulative hazard over time and observe whether the divergence, by strata, relative to the baseline hazard function (0 on the x axis) remains proportionately constant. This is illustrate below.



Another approach is to construct a "log-minus-log" plot. If the hazards remain constant through time the strata lines should remain constant. This is illustrated below.